Remarks/Arguments:

Claims 2, 9, 11 and 24-28 are pending in the application. Claims 2, 9, 11 and 27 are rejected. Claims 24-26 and 28 are withdrawn from consideration.

DETAILED ACTION

The Examiner acknowledges our amendment filed on January 12, 2007. The Examiner further acknowledges, contrary to what was stated in the Restriction Requirement, that claims 1-23 were not pending in the application and that claims 10, 23 and 14 were cancelled in the Preliminary Amendment filed February 23, 2006.

Applicants respectfully point out that it was in fact claims 10, **13** and 14 that were cancelled in the Preliminary Amendment.

The Examiner further states it is also acknowledged that Claims 1, 2-8, 10, 12-23 are cancelled and new claims 24-28 are added.

Applicants respectfully point out that it was in fact claims 1, **3**-8, 10 and 12-23 that stand cancelled and new claims 24-28 that were added in our previous response. Claim 2 remains pending in the application.

Restriction

Applicant's election without traverse of Group II (Claims 2 and 9) drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and a bisphosphonate in the reply filed on January 12, 2007 is acknowledged. As a single species, Applicants' election of pamidronic acid is also acknowledged. Claims 24-26 and 28 are withdrawn from consideration drawn to non-elected species. Claims 2, 9, 11 and 27 are examined on the merits in this application.

Applicants respectfully request, in view of the arguments presented below, that the Examiner searches the full scope of claim 2 and rejoins Claims 24-26 and 28. These claims clearly fall within the scope of claim 2 and thus the elected Group II: claims drawn to a combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and a bisphosphonate.

Objection-Specification

The specification is objected to for not having a specific arrangement and Applicants are requested to correct the error.

The Examiner states that the following guidelines illustrate the preferred layout for the specification of a utility application and that these guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

Applicants respectfully submit that 37 CFR 1.77(c) states:

(c) The text of the specification sections defined in paragraphs (b)(1) through (b)(12) of this section, if applicable, should be preceded by a section heading in uppercase and without underlining or bold type.

and point out that there is no legal requirement to insert non-applicable headings followed by the words "Not Applicable". That language is to be found in the MPEP under "608.01(a) Arrangement of Application [R-5]" which only discusses a *preferable* arrangement of the specification. This is not a legal obligation. Furthermore, the section headings quoted by the Examiner do not exactly correlate with 37 CFR 1.77(b). The appropriate section of the rule is copied below and Applicants have taken the following actions in accordance with this rule:

(b) The specification should include the following sections in order:

(1) Title of the invention, which may be accompanied by an introductory portion stating the name, citizenship, and residence of the applicant (unless included in the application data sheet).

> Not required because it was included in the Application Data Sheet see filed 23 Feb 2006 - see 37 CFR 1.77(b)(1), but already present.

(2) Cross-reference to related applications (unless included in the application data sheet).

Not required because it was included in the Application Data Sheet see filed 23 Feb 2006 - see 37 CFR 1.77(b)(1), but already present.

(3) Statement regarding federally sponsored research or development.

Not required.

(4) The names of the parties to a joint research agreement.

Not required.

*(5) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on a compact disc and an incorporation-by-reference of the material on the compact disc (see § **1.52(e)(5)**). The total number of compact discs including duplicates and the files on each compact disc shall be specified.*

Not required.

(6) Background of the invention.

Inserted as requested.

(7) Brief summary of the invention.

Inserted as requested.

(8) Brief description of the several views of the drawing.

Not required.

(9) Detailed description of the invention.

Inserted as requested.

(10) A claim or claims.

Already present.

(11) Abstract of the disclosure.

Already present.

*(12) "Sequence Listing," if on paper (see §§ **1.821** through **1.825**).*

Not required.

Rejection-35 U.S.C. 103

Claims 2, 9, 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janus et al (PG Pub 2002/0055457) in view of Curwen et al (Poster EORTC-NCI-AACR, 2002), Nelson et al (BJU International, 2000, 85(suppl 2), 45-48) and Walczak et al (Expert Opin. Investig. Drugs, 2002).

The Examiner discusses each one of these four references and concludes:

.. it would have been obvious to the ordinary skilled in the art to combine the bisphosphonate and endothelin receptor antagonist. There is a reasonable expectation of success, since bisphosphonate is used in treatment of prostate cancer and endothelin receptor antagonist (ZD4054) is used in treatment of prostate cancer, thus combining the two into a combination compound would show at least an additive effect. Additionally, the ordinary skilled artisans would be motivated to combine the teachings of the prior arts because Curwen et al teach that ZD4054 is a high-affinity ligand for the human ETA receptor, with a pIC_{50} value of 8.27, while ZD4054 had no measurable affinity for the ETg receptor. Furthermore, Janus et al teach that bisphosphonate addition impedes bone loss (see claim 8). Therefore, since ZD4054 is selective for ETA receptor, one would expect it to be active.

Applicants note that the Examiner had to combine the teachings of **four** references to arrive at the stated conclusions.

As the Examiner is no doubt aware, the USPTO bears the initial burden of establishing the *prima facie* case of obviousness and guidance is provided in the MPEP section 2143 where it is stated that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants respectfully point out that the Examiners combination argument fails at the first of these three basic criteria. In none of the four references cited is this motivation to combine even two of these references present.

Janus et al provides no teaching by way of data for dosing anything other than ABT-627 alone to patients. All of the examples in the application are for monotherapeutic treatment with this one compound. Applicants therefore conclude that Janus provides (i) no motivation to modify the reference by substituting ABT-627 for another compound or to combine reference teachings by

substituting one reference for another or even (ii) that there would be a reasonable expectation of success in such a combination.

The Examiner points to Curwen et al to provide the teaching of ZD4054. However, neither Curwen nor Janus provides the necessary motivation to make that combination of teachings. As stated above, Janus is silent as to the possibility of substituting the endothelin antagonist for another, non-disclosed, endothelin antagonist. Janus et al is further silent as to a combination with a bisphosphonate having particular beneficial effect and Curwen et al provides no teaching that ZD4054 would be an appropriate endothelin receptor antagonist for use in combination. No combinations are disclosed in Curwen et al. Curwen et al provides (i) no motivation to modify the reference by combining ZD4054 with another agent or to combine reference teachings by substituting one reference for another or even (ii) that there would be a reasonable expectation of success in such a combination.

Nelson et al discusses neither the concept of combination of endothelin antagonists with other agents, nor ZD4054 specifically, so it is difficult to see the relevance of this reference to the present invention. With respect to the three basic criteria for concluding an invention is obvious, Nelson et al provides (i) no motivation to modify the reference or to combine reference teachings by substituting one reference for another or even (ii) that there would be a reasonable expectation of success in such a combination.

Walczak et al provides no teaching other than Atrasentan as an endothelin antagonist. Specifically Walczak et al makes no mention of the possibility of substituting Atrasentan for ZD4054. Applicants respectfully point out that in addition, Walczak et al provides (i) no motivation to modify the reference or to combine reference teachings by substituting one reference for another or even (ii) that there would be a reasonable expectation of success in such a combination.

Therefore, with regard to the 103(a) objection, Applicants do not believe that the Examiner has established a *prima facie* case of obviousness. The Examiner asserts "it would have been obvious to the ordinary skilled in the art to combine the bisphosphonate and endothelin receptor antagonist". However, the Examiner has not provided credible reasons for this assertion.

The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "[T]he mere fact that the prior art could be so motivated would not have made the modification obvious unless the prior art suggested the desirability of the modification" (quoting *In re Gordon*, 733,

F.2d 900, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984)). Again we submit that the burden of proof rests with the Examiner and it is not acceptable to merely allege "it would have been obvious to the ordinary skilled in the art to combine ..." without supporting this allegation with evidence.

Applicants therefore respectfully request that the Examiner withdraws the 103(a) rejection.

In further support of the present invention Applicants draw the Examiners attention to reference 31 on the SB08 filed on 19th January: WILLIAMS, E.D., "The combination of a specific endothelin A receptor antagonist ZD4054 and submaximal bisphosphonate pamidronate prevents bone metastis," Poster Session, Angiogenesis and metastatasis inhibitors, 8 November 2006, European Journal of Cancer Supplements, page 15, Volume 4, No. 12, page 15. The Examiner has initialed this reference to show that it has been considered.

This reference has four authors, three from institutions in Australia and one from AstraZeneca, the assignee of the present invention.

This reference reports data obtained from a study analyzing the effect of ZD4054 and the bisphosphonate pamidronate, alone and in combination, on the formation of bone metastases. The results of this study were presented at an EORTC (European Organisation for Research and Treatment of Cancer) meeting in November 2006. The results of the study show that while treatment with either ZD4054 or pamidronate alone delayed the formation of bone metastases, mice receiving both agents were found to have no showing of any bone metastases.

There is no teaching or suggestion in any of the cited references that the combination of ZD4054 and bisphosphonate would result in such beneficial results, i.e., **no** bone metastases. These results appear to go beyond the "additive effect" discussed by the Examiner and thus provide further support of the patentability of the present invention.

We submit based on the arguments above and the results highlighted, that the combination of ZD4054 and a bisphosphonate is patentable.

Applicants therefore request that the rejection over 103(a) is withdrawn and that Claims 24-26 and 28 are rejoined and the Examiner proceeds to search the present invention as a whole, not just the elected species.

Applicants believe the application is in condition for allowance, which action is respectfully requested.

A petition for a 3 month extension of time is being filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101213-1P US.

Respectfully submitted,

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